Research Article

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The clinical significance of miR-590-3p in acute myeloid leukemia and potential regulatory mechanism based on bioinformatic prediction

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Abstract

Objectives: Acute myeloid leukaemia (AML) usually has a poor prognosis, and an effective prognostic marker is needed. MicroRNAs (miRNAs) have potential as prognostic markers. Therefore, the prognostic diagnostic role and potential regulatory mechanisms of miR-590-3p in AML were investigated.
Methods: 113 patients with AML and 83 healthy adults were included. miR-590-3p level was detected in AML patients before and after chemotherapy and in healthy adults using qRT-PCR. Correlating miR-590-3p levels with patient clinical data was assessed through the chi-squared test. The diagnostic potential of miR-590-3p was assessed by ROC curves. Survival of patients with different expression of miR-590-3p was assessed by Kaplan–Meier survival curves. COX regression analyzed the factors influencing the poor prognosis of AML. The potential pathways of miR-590-3p in AML progression were analyzed using GO and KEGG databases.
Results: In AML patients, miR-590-3p is upregulated, and miR-590-3p levels were notably decreased in complete remission after treatment. miR-590-3p has a good diagnostic value for AML. Patients with high miR-590-3p expression had shorter overall survival. And miR-590-3p was an independent influencing factor of poor prognosis in AML. miR-590-3p target genes are mainly enriched in the CDP-diacylglycerol biosynthesis process and the PI3K-Akt.
Conclusions: miR-590-3p has potential as a biomarker of poor prognosis in AML patients. miR-590-3p has the potential to modulate signaling pathways during AML development.

Keywords: acute myeloid leukemia; miR-590-3p; prognostic diagnostic value; potential regulatory mechanisms

Introduction

Acute myeloid leukaemia (AML) is a malignant disease caused by clonal expansion of abnormally differentiated primitive cells of the myeloid lineage [1, 2]. It has a high recurrence and mortality rate [3]. The annual incidence of AML in China is about 1.62/100,000, which ranks the highest in the incidence of leukaemia at 58.7 %, and the incidence of AML increases with age [4]. AML causes about 22,000 deaths annually. The main clinical manifestations of AML patients are anemia, hemorrhage and infection [5]. Approximately 54 % of AML patients diagnosed are >65 years of age, and the average age of patients presenting to the clinic is approximately 70 years [6, 7]. Patients' 5-year survival rate between the ages of 18 and 60 is about 40 %, but drops sharply to about 10 % for patients >60 years of age [8]. The general prognosis for AML is poor, and therefore the search for a validated prognostic biomarker is particularly important.

MicroRNA (miRNA) is an endogenous small non-coding ribonucleic acid. It can characterize the process of tumorigenesis and development more effectively than mRNA expression profiles. It can therefore be employed as an effective task for diagnosing and prognosticating human malignant neoplasms [9]. In addition, miRNAs can regulate cellular physiological activities of the organism as well as the bone marrow microenvironment. It regulates genes associated with hematopoietic stem cells and tumorigenesis [10].

Eight differentially miRNAs, including miR-590-3p, were found in the ceRNA network associated with AML prognosis [11]. In addition, previous research has demonstrated that

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miR-590-3p is associated with multiple myeloma (MM). And MM often develops or progresses to AML after treatment [12–16]. miR-590-3p can negatively affect the expression of TAZ in MM, thereby controlling the developmental process of multiple myeloma [17]. There is more evidence that miR-590 can promote cell proliferation and invasion in T-cell acute lymphoblastic leukaemia by inhibiting RB1 [18]. Unfortunately, the diagnostic role of miR-590-3p in AML and its regulatory mechanisms and prognostic value in AML have not been investigated; therefore, the aim of the present study was to assess the value of miR-590-3p in the clinical diagnosis of AML and the prognostic role of patients after treatment.

Materials and methods

Patients included

The Ethics Committee of the Dalian Municipal Friendship Hospital approved this study (No. 201524). The trials were conducted in accordance with the tenets of the Declaration of Helsinki, and all subjects and their families signed an informed consent form.

A total of 113 patients with first-episode AML attending Dalian Municipal Friendship Hospital between January 2016 and December 2018 were included. Inclusion criteria: a) fulfilling the diagnostic criteria for acute myeloid leukaemia; b) first clinical diagnosis of AML; c) no history of leukaemia and genetic metabolic disease; d) complete clinical data. Exclusion criteria: a) those with concomitant other hematological diseases; b) those with concomitant other malignancies; c) those with concomitant myelodysplasia. 87 cases were included in the same period of health check-ups. Patients with AML were followed up for 5 years after chemotherapy by telephone interviews and outpatient reviews; no cases were lost to follow-up and the survival rate of patients during the follow-up period was counted.

Collection of clinical data

Following French, AML patients were classified into three categories, American and British (FAB) criteria. AML patients were divided into three categories (poor, intermediate and good) according to European Leukemia Network (ELN) risk. Complete remission (CR) was defined as: a) less than 0.5 % primitive cells in the bone marrow; b) normal peripheral blood counts after 4 weeks of induction therapy; and c) no residual extramedullary disease. Induction therapy was administered according to the patient's clinical status. Specific treatment options for AML are described in the NCCN Clinical Practice Guidelines in Oncology.

The age and sex of the patients were recorded. In addition, 5 mL of fasting venous blood was obtained from all subjects. White blood cell count (WBC), hemoglobin (HB), and platelet count (PLT) were also analyzed and collected from all subjects.

Detection of miR-590-3p expression in serum by qRT-PCR

1 mL of Trizol (Ambion, USA) reagent was added to extract RNA and reverse transcribed to cDNA by a reverse transcription kit (Takara, Japan). cDNA was used as a template to detect miR-590-3p expression in serum samples by qRT-PCR, with U6 as an endogenous reference. The experimental conditions were 95 °C pre-denaturation for 15 min; 1 cycle, 95 °C denaturation for 15 s; 65 °C annealing extension for 45 s; a total of 40 cycles. The miR-590-3p level was calculated ($2^{-\Delta\Delta Ct}$ method). The primer sequence for miR-590-3p is as follows: forward 5′-TAATTTTATGTATAAGCTAGT-3′, reverse 5′-GTG CAGGGTCCGAGGT-3′; U6 forward 5′-CTCGCTTCGGCAGCA CA-3′, reverse 5′-AACGCTTCACGAATTTCGCT-3′.

Prediction of downstream target genes

miRDB, Targetscan and miRWalk databases to predict miR-590-3p downstream target genes. Utilizing the bioinformatics platform, we conducted Gene Ontology (GO) annotation and Kyoto Encyclopedia of the Genome (KEGG) pathway enrichment analysis by inputting overlapping targets and specifying "*Homo sapiens*" as the organism of interest. Subsequently, we filtered the results to obtain the most significant GO annotations and KEGG signaling pathways based on the information richness within each entry.

Statistics and analyses

SPSS 25.0 was applied for analyzing the data. All results are presented as average ± SD and t-test was applied between groups. Kaplan–Meier survival curves were used to assess patient survival and independent factors affecting AML were analyzed using COX. Chi-squared test was used to correlate miR-590-3p expression with clinical data. ROC curves were applied to analyses the diagnostic role of miR-590-3p in AML patients, and a meaningful difference was defined as a p-value<0.05.

Results

Comparison of subjects' clinical data

As indicated in Table 1, no statistically notably difference in age and gender was found between the two groups of subjects (p>0.05). There were considerable differences in WB, HB, and PLT (p<0.001). BM Blasts in AML patient was 61.51 ± 22.08. According to FAB staging, there were 12 patients with type 0, 64 patients with type 1/2 and 37 patients with type 4/5. According to the ELN risk, 33 of the AML patients were in the Favorable risk group, 23 were in the Adverse risk group, and 57 were in the Intermediate risk group. 54 of the AML patients were in complete remission after chemotherapy and 59 did not achieve complete remission.

miR-590-3p level and its diagnostic value

miR-590-3p level was noticeably higher in AML than control (p<0.001, Figure 1A). The diagnostic significance of miR-590-3p for AML was predicted through the ROC curve, and the AUC was 0.861 (95 % CI 0.810–0.913) with a sensitivity of 71.70 % and a specificity of 94.30 % (Figure 1B).

Table 1: Clinical data of the study subjects.

Indicators	Control group (n=87)	AML group (n=113)	p-Value
Age, years	56.60 ± 17.73	55.21 ± 19.05	0.597
Gender			0.623
Male	50	61	
Female	37	52	
WBC, $\times 10^9$/L	6.11 ± 1.91	40.46 ± 32.76	0.000
HB, g/dL	130.16 ± 16.89	72.38 ± 17.56	0.000
PLT, $\times 10^5$/μL	196.58 ± 24.79	50.06 ± 17.13	0.000
BM blasts	/	61.51 ± 22.08	/
FAB			
0	/	12	/
1/2		64	
4/5		37	
ELN risk			
Favorable	/	33	/
Adverse		23	
Intermediate		57	
Complete remission			
Yes	/	54	/
No		59	

WBC, white blood cell; HB, hemoglobin; PLT, platelet; BM, bone marrow; FAB, French–America–British; ELN, European leukemia network.

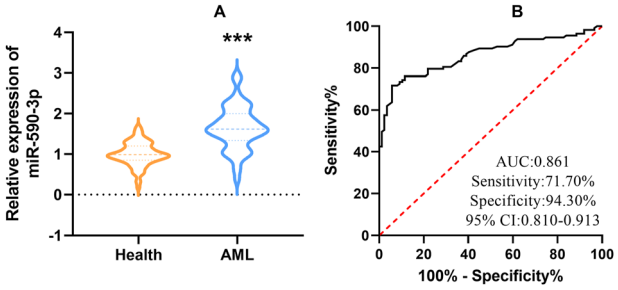

Figure 1: miR-590-3p level in AML patients and its diagnostic value. **A** miR-590-3p is expressed at higher in acute myeloid leukaemia (AML) than in health (***p<0.001); **B** miR-590-3p may be a marker for the diagnosis of AML.

Correlation between miR-590-3p expression levels and clinical indicators in subjects

The miR-590-3p expression level in AML was significantly correlated with BM Blasts, ELN risk groups, and the presence or absence of complete remission after treatment (p<0.05), independently of other factors such as age, gender, WBC and HB (p>0.05, Table 2).

miR-590-3p level of AML after chemotherapy

After chemotherapy, serum of miR-590-3p were measured in AML patients. Of 113 AML patients, 54 achieved CR and 59 did not achieve CR. Compared with pre-treatment, the levels of miR-590-3p were notably lower in the CR group of patients after treatment, but the levels of miR-590-3p did not notably differ in the non-CR group (Figure 2A and B). In addition, patients in the CR group had significantly lower miR-590-3p levels both before and after treatment compared to the non-CR group (Figure 2C and D). The data indicate that miR-590-3p levels are highly correlated with the efficacy of chemotherapy in AML patients, and that a significant decrease in miR-590-3p levels may indicate a good response to chemotherapy, the achievement of complete remission.

Prognostic value of miR-590-3p

Figure 3 shows the effect of miR-590-3p expression on the survival of AML patients. AML patients with high miR-590-3p expression have shorter overall survival (Log-rank p=0.0003). Furthermore, in a multifactorial Cox survival analysis, miR-590-3p was found to be an important factor for the prognosis of AML patients. miR-590-3p high-expressing patients were 1.901 times more likely to have a

Table 2: Correlation between miR-590-3p expression levels and clinical characteristics in AML patients.

Indicators	Total	Low miR-590-3p expression (n=56)	High miR-590-3p expression (n=57)	p-Value
Age, years				0.764
≥60	48	23	25	
<60	65	33	32	
Gender				0.110
Male	61	26	35	
Female	52	30	22	
WBC ($\times 10^9$/L)				0.483
≥10	84	40	44	
<10	29	16	13	
HB, g/dL				0.110
≥72.38	52	30	22	
<72.38	61	26	35	
PLT ($\times 10^5$/μL)				0.218
≥50	60	33	27	
<50	53	23	30	
BM blasts				0.019
≥50	80	34	46	
<50	33	22	11	
FAB				0.505
0	12	5	7	
1/2	64	31	33	
4/5	37	20	17	
ELN risk				0.012
Favorable	33	19	14	
Intermediate	57	31	26	
Adverse	23	6	17	
CR				0.001
No	59	20	39	
Yes	54	36	18	

WBC, white blood cell; HB, hemoglobin; PLT, platelet; BM, bone marrow; FAB, French–America–British; ELN, european leukemia network; CR, complete remission.

poor prognosis than low-expressing patients (p=0.025, HR=1.901, 95 % CI: 1.084–3.332; Table 3).

miR-590-3p is involved in multiple signaling pathways

Figure 4A reacts to the downstream target genes of miR-590-3p screened by three databases, with 41 overlapping genes. To elucidate the possible mechanisms of gene-target interactions, GO and KEGG enrichment analyses were performed. In GO enrichment analyses, the main biological process (BP) was predominantly enriched for condensed extrachromosomal filaments, while categories of cellular components (CC) were mainly enriched in the glycerol ester synthesis process, CDP-diacylglycerol biosynthetic process,

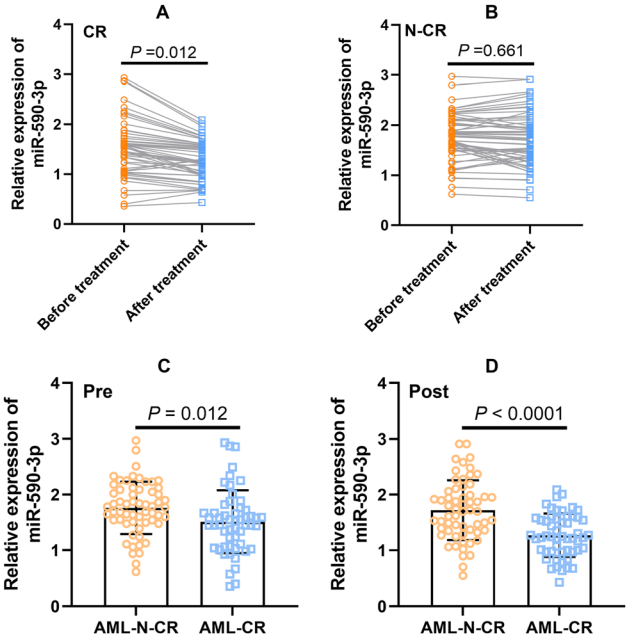

Figure 2: miR-590-3p levels before and after treatment. **A** For AML cases that achieved CR, miR-590-3p levels in blood samples were notably lower after treatment; **B** For patients in incomplete remission, there was no notable change in miR-590-3p levels after treatment; **C** and **D** Serum miR-590-3p were notably lower in AML patients that achieved CR than those that did not achieve CR, both before and after treatment.

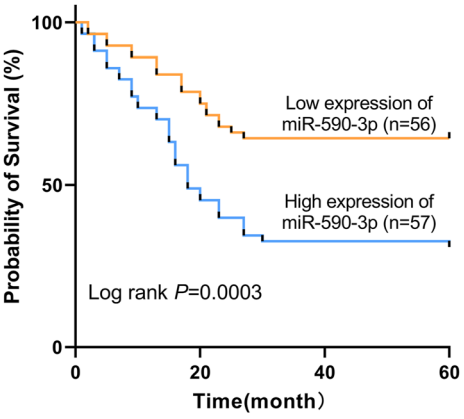

Figure 3: Kaplan–Meier curves were used to evaluate the prognostic significance of miR-590-3p in AML patients over five years. Patients exhibiting high miR-590-3p expression demonstrated a reduced overall survival in comparison to patients with low expression (log-rank test p=0.0003).

and the molecular function (MF) was predominantly enriched for phosphatidylinositol 3-phosphatase activity (Figure 4B). To delve deeper into the biological mechanisms underlying the overlapping targets, we conducted KEGG enrichment analysis. As illustrated in Figure 4C, Oocyte meiosis, TGF-β signaling pathway, and PI3K/AKT signaling

Table 3: Multivariate COX analysis of factors associated with patients with AML.

Characteristics	Multivariate analysis		
	p-Value	HR	95 % CI
miR-590-3p	0.025	1.901	1.084–3.332
Age	0.031	1.873	1.060–3.309
Gender	0.611	1.151	0.669–1.983
WBC	0.377	1.398	0.665–2.939
HB	0.278	1.366	0.778–2.397
PLT	0.864	1.046	0.623–1.757
BM blasts	0.030	2.348	1.086–5.077
FAB	0.743	1.098	0.629–1.915
ELN risk	0.036	1.866	1.040–3.346

pathway, etc. were among the top 10 enriched pathway for miR-590-3p overlapping targets.

Discussion

AML is characterized by impaired differentiation of primitive cells and uncontrolled proliferation and is one of the most common forms of acute leukemia in the adult population [19]. In recent years, the morbidity and mortality rates of AML have increased [20]. Clinical treatment is based on chemotherapy, however, some patients have drug resistance, poor therapeutic efficacy, easy to relapse in the prognosis, which seriously threatens patients' lives [21]. In addition, age also affects the prognosis of AML patients, with older patients having a shorter 5-year postoperative survival and a poorer prognosis [22]. We urgently need a more effective biomarker for the early detection, diagnosis and prevention of AML.

Several reports have indicated that miRNAs are aberrantly expressed in cancers and can be applied as clinical prognostic and diagnostic markers [23–25]. Eight aberrantly expressed miRNAs were reportedly found in the ceRNA network associated with AML prognosis, including miR-590-3p [11]. The levels of miR-590-3p in serum were markedly increased in AML patients than in healthy, indicating that miR-590-3p plays a part in the disease advance of AML and is associated with the prognosis of AML. Further analysis showed that those expressing high miR-590-3p levels had a markedly reduced survival. miR-590-3p levels were notably

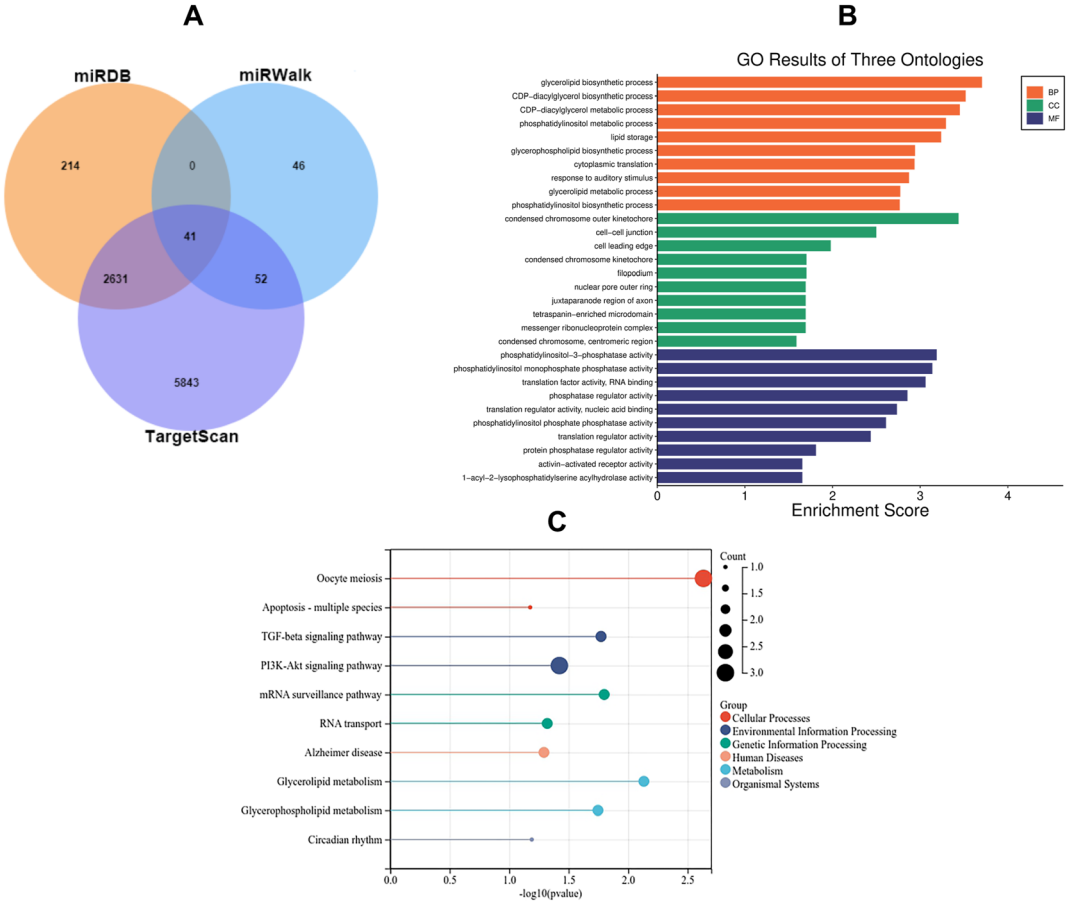

Figure 4: Possible signaling pathways involved in downstream target genes of miR-590-3p. **A** miR-590-3p downstream target genes predicted by three databases, miRDB, miRWalk, and Targetscan; **B** Go enrichment analysis was employed to explore the overlapping targets; **C** Signaling pathways predicted by the KEGG database to be predominantly enriched for target genes.

lower in AML with complete remission after treatment, suggesting that miR-590-3p plays an essential function in the advance of AML. In addition, miR-590-3p was a risk factor for predicting poor prognosis of AML. miR-590-3p had an AUC of 0.810 for the diagnosis of AML, indicating that miR-590-3p has a better diagnostic and prognostic value for AML, and is expected to become a biomarker for poor prognosis of AML. This provides further evidence that miR-590-3p linked to AML inception and growth.

miRNAs can be involved in various biological responses by post-transcriptionally regulating the expression of target genes [26]. The Venn diagram shows 41 target genes that overlap in three databases. CDP-diacylglycerol biosynthesis phosphatidylserine (PS), phosphatidylethanolamine (PE) [27]. PS externalization is a hallmark of apoptosis in AML cells [28]. Our results showed that 41 target genes downstream of miR-590-3p were mainly enriched in CDP-diacylglycerol biosynthesis and metabolism process, and it was speculated that it might be possible that miR-590-3p is involved in regulating CDP-diacylglycerol biosynthesis process and controlling PS production and externalization, and thus involved in the progression of AML. Brigger et al. demonstrated that phosphatidylinositol (WIPI) expression levels are elevated in leukaemia [29]. Phosphatidylinositol (PtdIns), which is phosphorylated by a variety of lipid kinases, produces phosphatidylinositol 3-phosphate (PI3P) [30], it is associated with the process of cellular autophagy in AML [31, 32]. Typically, WIPI members are essential PI3P effectors in autophagy [33]. Our results show that miR-590-3p downstream target genes are mainly enriched in phosphatidylinositol metabolism processes and the activation and control of phosphatidylinositol 3-phosphatase (PI3P phosphatase) activity. It is suggested that miR-590-3p may be involved in the cellular autophagy process associated with AML by regulating the interaction between WIPI and PI3P. In addition, the PI3K-Akt signaling pathway has been shown to have important effects on cell growth and apoptosis. When the PI3K-Akt pathway is activated, cell proliferation and apoptosis programs are disrupted, promoting tumor cell growth [34–36]. The PI3K-Akt pathway is frequently activated in patients with AML, resulting in reduced patient survival has been recognized [37]. And in this study, we found that miR-590-3p target genes were primarily accumulated in the PI3K-Akt pathway, suggesting that miR-590-3p may contribute to AML initiation and evolution by regulating the PI3K-Akt pathway.

However, we must admit that there are some limitations in this study: firstly, the regulatory role of miR-590-3p in AML needs more experimental models (e.g., cellular experiments, animal experiments, etc.) to be further verified; secondly, the signaling pathways of miR-590-3p downstream target genes analyzed by databases also need to be further verified by experiments.

In conclusion, miR-590-3p is highly expressed in AML patients, and serum levels of miR-590-3p were significantly decreased in AML patients in complete remission after treatment. miR-590-3p has great potential as a diagnostic marker for poor prognosis in AML. In addition, miR-590-3p may be involved in the PI3K-Akt signaling pathway through post-transcriptional regulation of the expression of target genes, thus affecting the progression of AML.

Research ethics: The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Dalian Municipal Friendship Hospital before the study began (No. 201524).
Informed consent: The written informed consent has been obtained from the participants involved.
Author contributions: Conceptualization, L.M.; Data curation, L.M., D.Q. and X.C.; Formal analysis, A.Y. and X.Z.; Funding acquisition, L.M.; Investigation, A.Y. and X.Z.; Methodology, L.M., D.Q. and X.C.; Project administration, L.M.; Resources, A.Y. and X.Z.; Software, A.Y. and X.Z.; Supervision, L.M.; Validation, D.Q. and X.C.; Visualization, D.Q. and X.C.; Roles/Writing – original draft, L.M.; Writing – review & editing, L.M., D.Q., X.C., A.Y. and X.Z.
Use of Large Language Models, AI and Machine Learning Tools: Not applicable.
Conflict of interest: There is no conflict of interest in this study.
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Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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